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Synthesis and Stereochemistry of Stereoisomeric 1,3-Oxazino- and 1,3-Thiazino[4,3-*a*]isoquinolines[1)]

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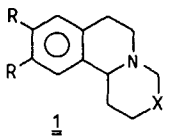
Starting from the 6,7-dialkoxy-1-[bis(hydroxymethyl)methyl]-1,2,3,4-tetrahydroisoquinolines **2** and **3**, the 4-imino-substituted 1-(hydroxymethyl)-9,10-dialkoxy-2*H*,4*H*-1,6,7,11b-tetrahydro-1,3-oxazino- and -thiazino[4,3-*a*]isoquinoline diastereomers **6a–c**, **7a–c**, **8a–c**, **9a–c**, **14**, and **15** and the 4-substituted 1,6,7,11b-tetrahydro-1,3-oxazino[4,3-*a*]isoquinoline diastereomers **16–24** were prepared. The relative configurations and the predominant conformation of these products were determined by NMR spectroscopy and for **18** by X-ray diffraction methods. The prepared 1,3-oxazino[4,3-*a*]-isoquinoline diasteromers have predominantly *trans* conformations (**16**, **18**, **22**, **23**), whereas *cis* conformations (*cis*-**A**) prevail for **20**, **21** and **24**. Thus, the first evidence for either *trans*- or *cis*-**A** conformations in 1,3-oxazino[4,3-*a*]isoquinolines is presented.

The tetrahydroisoquinoline-condensed 1,3-heterocycles of type **1** (X = O, S, NH) belong to the important family of simple tetrahydroisoquinolines. The pyrimido[6,1-*a*]isoquinolines **1** (X = NH), prepared mainly for pharmacological purposes, have been thoroughly studied[2)]. In this series, 2-(mesitylimino)-3-methyl-9,10-dimethoxy-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one (Trequinsin) has recently been developed as an antihypertensive agent[3)]. On the other hand, only a few papers[4–8)] deal with the synthesis of the closely analogous 1,3-oxazino- and 1,3-thiazino[4,3-*a*]isoquinolines **1** (X = O, S).



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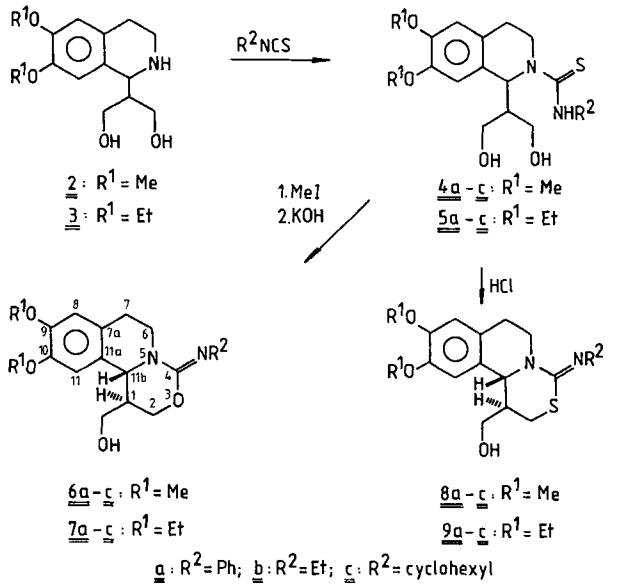
The first synthesis of the 1,3-oxazino[4,3-*a*]isoquinoline ring system was performed by Openshaw and Whittaker[4)]. Most later syntheses made use of 1,3-difunctional isoquinoline derivatives[5)], but the cycloaddition of 3,4-dihydroisoquinolines and ketenes has also been applied[6)].

We now report on the synthesis of 1,3-oxazino- and 1,3-thiazino[4,3-*a*]isoquinolines. These compounds are interesting from both pharmacological[9)] and stereochemical points of view. Their structures are related to those of pharmacologically effective compounds, e.g. Debrisoquin and other systems[10)]. Our aim was to prepare the diastereomers of the title compounds and to study their conformations.

Results and Discussion

A synthesis of 1-[bis(hydroxymethyl)methyl]-6,7-dimethoxy- and -6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline (**2**, **3**), involving treatment of 6,7-dialkoxy-3,4-dihydroisoquinoline with formaldehyde, followed by reduction, has recently been reported[11)]. Compounds **2** and **3** and suitable starting materials for the synthesis of the title compounds. The

Scheme 1



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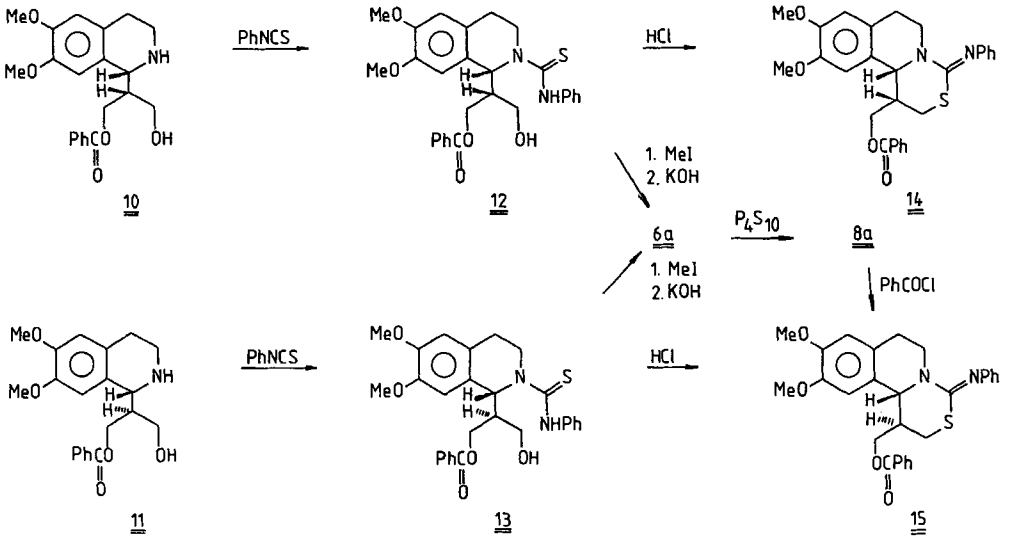
Scheme 2



reaction of **2** or **3** with phenyl, ethyl, or cyclohexyl isothiocyanate provided the thioureas **4a–c** and **5a–c** in good yields. The methyl iodide reaction of **4a–c** and **5a–c**, followed by thiomethanol elimination on alkali treatment, gave the 1,3-oxazino[4,3-*a*]isoquinolines **6a–c** and **7a–c**. When the thioureas **4a–c** and **5a–c** were heated at reflux with ethanolic hydrogen chloride, the 1,3-thiazino[4,3-*a*]isoquinolines **8a–c** and **9a–c** were formed (Scheme 1).

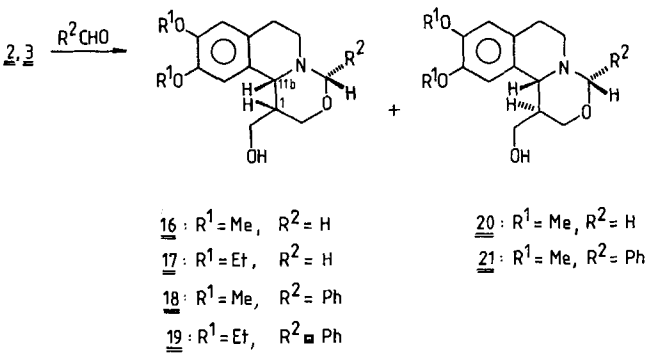
Spectroscopic investigations indicated that the prepared compounds **6–9** are stereohomogeneous: only a single diastereomer could be detected in the crude product[12]. Besides the spectroscopic evidence, the relative configurations of the products were determined by configurative correlation.

The *threo*- and *erythro-O*-acyl derivatives **10** and **11** have already been synthesized earlier[13] from the *N*-benzoyl derivative of **2** by N→O acyl migration and fractional crystallization of the isomers formed[13]. After phenyl isothiocyanate addition, compounds **10** and **11** gave adducts **12** and **13**. Ethanolic hydrogen chloride treatment of the *threo* isomer resulted in the *cis*- (**14**), while treatment of the *erythro* isomer afforded the *trans*-1,3-thiazine derivative (**15**). Since the benzoylation of **8a**, prepared as in Scheme 1, led to the same product as was obtained from the *erythro* series, **8** and **9** must possess *trans* relative configurations.

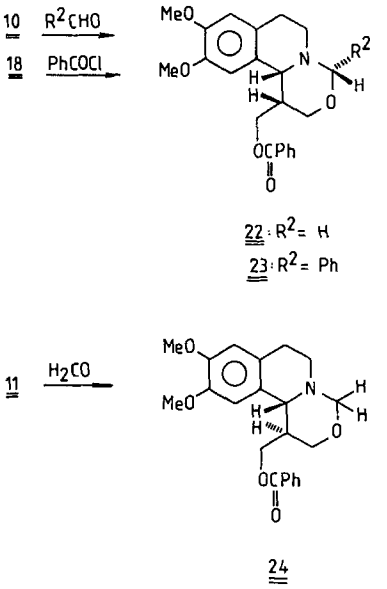
The treatment of *threo*- (**12**) and *erythro*-thioureas (**13**) with methyl iodide and subsequently with alkali gave the same product **6a**, since debenzoylation and ring closure took place in this process. The relative configurations of 1,3-oxazines **6** and **7** were confirmed chemically by O/S exchange, starting from **6a**, resulting in **8a** with *trans* relative configuration, because the starting oxazine also has the *trans* relative configuration (Scheme 2).

Ring closure of amino alcohols **2** and **3** with formaldehyde and benzaldehyde was found to proceed stereoselectively. Besides the major products **18** and **20**, the C-1 epimers **16** and **21** were found in 5–15% yield in the crude reaction products. Isolation of the minor C-1 epimer **21** was also successful.

Scheme 3



Structure elucidation by means of the configurational correlation discussed earlier was attempted starting from **10** and **11**. With formaldehyde, these compounds gave the C-1 epimers **22** and **24**, respectively, containing 1-H and 11b-



H in the *cis* or *trans* position. The ring-closure reaction with benzaldehyde was successful only in the reaction of **10** yielding **23**. In contrast, the reaction of **11** with benzaldehyde furnished only the oxazine **18** and the benzoate salt of the starting amino alcohol **2**.

Though the benzoylation of **18** provided the benzoyloxy derivative **23** in excellent yield, the possibility of very facile epimerization[14,15] makes this reaction of limited use for the structural determination.

Spectroscopic Investigations

The most important IR, ^{1}H-, and ^{13}C-NMR data confirming the structures of the new compounds are given in Tables 1 and 2 for one representative of each type.

The NMR data on the imino-substituted oxazines and thiazines **6a**, **8a**, **14***, and **15** are very similar (allowing for the effects arising from the substituents on C-1 and the effects of the O/S exchange) which supports the similar stereostructures of these compounds.

The analogous stereostructure is related to the flexibility of these compounds and a consequence of the electron delocalization within the N–C(=N)–X (X = S, O) group. The planar or nearly planar N-5 bonding permits free pseudorotation of the hetero rings at room temperature. Because of the low energy barrier of this conformational movement, only the partial conformation around C-1 and C-11b can be derived from the NMR data.

For the determination of the configurations around C-1 and C-11b, the vicinal proton-proton coupling constant ^3J(1-H, 11b-H) is informative[16]. If these protons are in the *trans* position (in accordance with the dihedral angles of 180°), this coupling constant is much higher than for the *cis* isomer (dihedral angle of 60°). Thus, the configurations of **6a**, **8a**, and **15** are *trans*, while that of **14** is *cis*, as supported by the coupling constants of 4.5, 8.0, 8.2, and 3.7 Hz, respectively, in accordance with the preparative results.

The coupling constant for **6a** is smaller than that for the analog **8a**, which may be explained by the stronger –I effect of the carbamide group than that of the thiocarbamide[17a] and by the distortion in the dihedral angle 1-H–C–C–11b-H due to the shorter C-4–O bond (the longer C-4–S bond in **8a** allows this angle to be nearer to 180°). A comparison of the NMR data of the isomers **14** and **15** reveals that 2-H and 11b-H are more shielded in the *trans* isomers **15**, while the shielding of α-H_2 atoms changes in the opposite sense relative to the *cis* compounds. The reason for this is that in the *trans* isomer the aromatic ring of the *equatorial* benzoyloxymethyl group shields 11b-H and 2-H, while the methylene hydrogen atoms of the hydroxymethyl group at C-1 are coplanar with the condensed benzene ring; thus, the anisotropic effect[17b] of the latter is manifested in a paramagnetic shift.

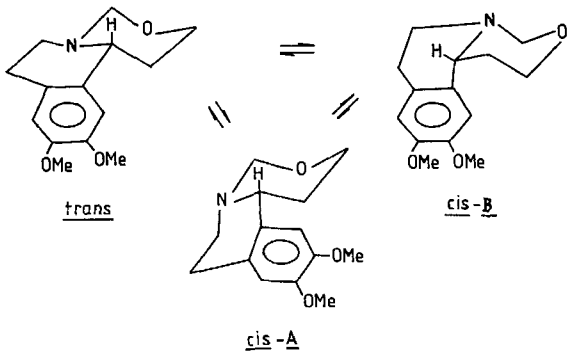
*) In spite of the *cis* position of 1-H and 11b-H, the mean dihedral angle is not significantly different as compared to **15** with *trans* configuration due to free pseudorotation of the hetero ring strained by the N–C(=N)–S moiety.

Due to the steric compression shift[18] arising from the sterically hindered *axial* benzoyloxymethyl group, the carbon chemical shifts of C-α and C-11 are smaller in the *cis* than in the *trans* isomer. The other ^{13}C-NMR chemical shifts for the two isomers agree within 1 ppm.

For compounds **16**–**24**, containing a perhydrooxazine ring, the possible N-5 inversion[19,20] has also to be taken into account besides the C-1, -4, -11b configurations and conformations of the two annelated hetero rings. The steric structure of these molecules is determined by the steric interactions of the substituents at C-1 and – in the 4-phenyl-substituted derivatives – C-4, as well as by the interaction of the 6-methylene group. Assignment of this dominant stereostructure needs not only a comparative evaluation of meaningful chemical shifts and coupling constants but also the measurement of nuclear Overhauser effects, which are directly connected with the proximity in space[21]. Hence, we carried out two-dimensional NOE experiments[22] for the diastereomeric pairs **16**/**20** and **18**/**21** after unambiguous assignment of the coupling network by means of the usual H,H-COSY spectra[23]. After dissolution in $CDCl_3$, the separately prepared stereohomogeneous 1-hydroxymethyl derivatives **18**, **20**, and **21** yield within only a few minutes an equilibrium diastereoisomeric mixture through temporary opening of the oxazine ring[14,15]. To overcome this unfavourable phenomenon, we studied these compounds immediately after dissolution in CD_3OD, in which the above process is much slower. The spectroscopic parameters and stereostructure of **16** were subtracted by investigation of the equilibrium mixture **20**/**16**.

The crystal structure of **18** was also determined by X-ray diffraction (Figure 1). In agreement with the diffraction data, the relative configurations of **16**, **18**, **20**, and **21** could be assigned as depicted in Scheme 3, taking into account the coupling constants J(1-H, 11b-H) and J(1-H, 2-H_{ax}) and the characteristic NOE interactions. In **16** and **18** the predominant ring annelation is *trans*, while in **20** and **21** it is *cis* with „*cis*-**A**" predominant conformation (Scheme 4), and with an *equatorial* 4-phenyl group in **18** and **21**, in accordance with the assigned NOEs and large steric compression shifts[18] for C-1, C-6, and C-8.

Scheme 4



The ^{1}H- and ^{13}C-NMR spectral data of benzoyl derivatives **22**–**24** are completely analogous to those of their par-

ent compounds discussed above, and consequently not only their relative configurations, but also their predominant conformations should be the same.

Crabb et al.[5b,c] considered three similar conformations for 4-(*p*-nitrophenyl)-1,6,7,11b-tetrahydro-2*H*,4*H*-[1,3]oxazino-[4,3-*a*]isoquinoline. Supposing an *equatorial* *p*-nitrophenyl substituent, they concluded, on the basis of the weak Bohlmann bands[24] and the 1,11b vicinal couplings, that the predominant conformation was *cis*-**A**, and consequently 11b-H and 4-H were in *cis* position.

Since no other data on the stereochemistry of 1,3-oxazino-[4,3-*a*]isoquinolines are available in the literature, our observations are the first evidence for the presence of either *trans*- or *cis*-predominant conformations.

X-ray Analysis of Oxazinoisoquinoline 18

Figure 1 depicts a perspective view of the molecular structure computed from the atomic coordinates listed with their e.s.d.'s in Table 4.

The 1-CH_2OH moiety assumes the β-*axial* orientation as shown by the corresponding torsion angles C(12)–C(1)–C(11b)–N(5) = −65.8(3)° and C(12)–C(1)–C(2)–O(3) = 68.4(3)°. The 1,3-oxazine ring (C) has a chair conformation which has little influence on the conformation of ring **B** by their *trans* junction. In contrast to azeto[2,1-*a*]isoquinolines[13], ring **B** in **18** possesses an almost perfect half-chair conformation with a C_2 axis bisecting the N(5)–C(6) bond with a rather low asymmetry factor[25] [$f(C_2)$ = 3.6 pm]. The corresponding puckering parameters[26] are Q = 0.534(2) Å, Θ = 51.1(3)° and γ = 36.1(3)°. The 4-phenyl group is attached β-*equatorially* to the oxazine ring, with C(13)–C(4)–N(5)–C(11b) = −175.9(4)°. The extent of rotation about the C(4)–C(13) bond can be given by the torsion angles: C(14)–C(13)–C(4)–N(5) = −65.0(4)° and C(14)–C(13)–C(4)–O(3) = 55.3(4)°. This means that the best plane of the phenyl ring practically bisects the O(3)–C(4)–N(5) angle of 109.2(3)°.

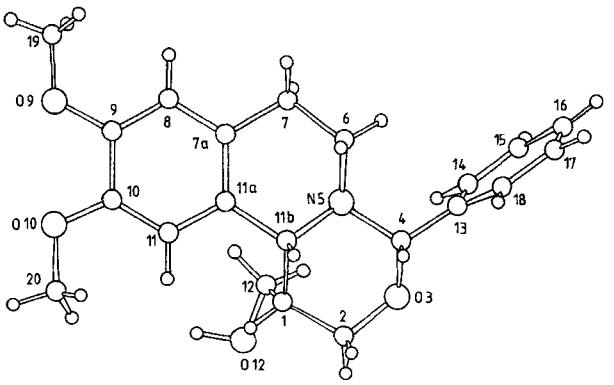


Figure 1. A perspective view of the molecular structure of **18** with atomic numbering; the bare numbers are for carbon atoms unless indicated otherwise; the hydrogen atoms are shown but not labelled

The hydroxy group forms an intermolecular hydrogen bond with the ether oxygen O(10) of one of the methoxy groups, which is rather rare. The parameters of this hydrogen bond are as follows.

D–H···A	D···A	H···A	∢D–H···A
O(12)–H(12)···O(10) [2 − *x*, 1 − *y*, 1 − *z*]	3.007(2) Å	2.047(2) Å	157.4(2)°

Table 1. Characteristic IR bands in KBr [cm^{-1}] and ^{1}H-NMR data (δ_{TMS} = 0, *J* [Hz]) of compounds **6a**, **8a**, **14**–**16**, **18**, and **20**–**24** at 250 MHz[a]

Compound	$\tilde{\nu}_{OH}$ or $\tilde{\nu}_{C=O}$[b] band	1-H m (1 H)	2-H_2 (2 dd[c], 2 x 1 H)	∝-H_2 (2 dd[c], 2 x 1 H)	4-H_2 (s/2 d, 1 H/2 H)[d]	11b-H (d, 1 H) J(1,11b)	8-, 11-H (2 s, 2 x 1 H)
6a	ca. 3125	ca. 3.7[e]	ca. 3,7[e] ca. 4.3[g]	ca. 4.05[f]	–	4.40 (4.5)	6.67 6.87
8a	ca. 3175	ca. 2.7[g]	ca. 2.9[h] ca. 3.1[h]	ca. 3.85[e]	–	4.60 (8)	6.72 6.74
14	1713	4.65[g]	ca. 3.05[h]	4.10 4.28(t)	–	5.00 (3.2)	6.62 6.66
15	1718	ca. 4.55[e]	2.7 – 3.3[h]	ca. 4.55[e,f]	–	4.75 (8.2)	6.72 6.74
16		ca. 2.1[g]	3.75 4.33(d)	3.25 3.83(t)	4.0 4.49	3.74 (<2)	6.69 6.80
18	ca. 3465	ca. 2.3[g,h]	3.98(d)[e] 4.42(d)	3.35(d) 4.08(t)	4.72	3.95[e] (<2)	6.63 6.85
20	ca. 3420	ca. 2.1[g]	3.74(t) 4.07	3.52 3.66	4.53 4.58	4.12 (10.5)	6.72 6.89
21	ca. 3465	2.22[g]	3.99(t) 4.31[e]	3.63 3.71	4.82[j]	4.33[e] (10.7)	6.68 6.87
22	1724	2.55[g,h]	3.85(d)[e] 4.36(d)	4.28 4.58(t)[i]	4.03 4.58[i]	3.78 (<2)	6.60 6.80
23	1720	2.65[g,h]	ca. 4.0(d)[e] 4.45(d)[i]	4.45[i] 4.80(t)	4.71	3.97[e] (<2)	6.55 6.88
24	1724	2.52[g]	ca. 4.2[e]	ca. 4.35[f]	4.62 4.68	4.21[e] (10.8)	6.51 6.65

[a] Solvent: [D_6]DMSO (**6a**), $CDCl_3$ (**8a**, **14**, **15**, **22**–**24**) or CD_3OD (**16**, **18**, **20**, **21**). The assignments of the individual signals were proved by DR measurements for compounds **18**, **20**, and **21** and also by 2D-COSY (**18**) and 2D-NOESY (**18** and **21**) experiments; $\nu_{C=N}$ band: $\tilde{\nu}$ = 1565–1585 cm^{-1} (**6a**, **8a**, **14**, **15**). Other signals: 9-, 10-OCH_3: δ = 3.67–3.91 (2 s, 2 × 3H). – [b] Ester carbonyl of **14**, **15**, and **22**–**24**; $\nu_{C=O}$ (ester) bands: $\tilde{\nu}$ = 1265–1275 and 1110–1120 cm^{-1}. – [c] A or B part of an ABX system; *J*(A,B) = 10–12 Hz, *J*(A,X) and/or *J*(B,X) = 3–6 Hz; „t" (dd → t) if *J*(A,X) ≈ *J*(A,B) or *J*(B,X) ≈ *J*(A,B); „d" (dd → d) if *J*(A,X) or *J*(B,X) < 2 Hz. – [d] AB-type spectrum: (2 d, 2 × 1H) for **20**, **22**, and **24**; *J*(A,B) = 10.5, 8.2, and 11 Hz, respectively. – [e,i] Overlapping signals. – [f] AB part of an ABX system near the A_2X limiting case („s"). – [g] Unresolved m. – [h] Overlapped by the 6-, 7-H m's appearing at δ = 2.1–3.6 for the compounds investigated. – [j] Overlapped by the water signal of the solvent.

Table 2. ^{13}C-NMR chemical shifts (δ_{TMS} = 0) of compounds **6a**, **8a**, **14**, **15**, **18**, **20**–**24** at 20 (for **6a**, **8a**, **14**, **15**) or 63 MHz (**16**, **18**, **20**–**24**)[a]

Compound	C-2	C-4	C-6	C-7	C-α	C-1	C-11b	C-8, -11		C-7a, -11a	
6a	66.4	151.8[c]	45.8	28.1	62.7	43.3[d]	56.4[b]	111.1	114.4	129.6[e]	131.1
8a	28.6[f]	156.2	46.1	28.6[f]	63.0	44.2	58.7	110.7	112.5	127.8	129.5
14[g]	29.9[b]	155.6	42.9	28.9[b]	63.4	41.5	58.9	110.0	111.9	125.7	128.6
15[g]	29.0[b]	155.8	42.4	28.6[b]	65.1	45.8	58.7	110.5	112.4	127.2	129.7
16[b]	70.0	88.2	47.5	29.4	60.0	42.5	63.5	109.4	113.3	128.7	128.5
18[g]	69.7	98.6	46.5	29.7	60.2	42.3	65.2	109.6	113.2	128.9	129.3
20[g]	71.3	86.6	44.1	29.4	61.4	38.4	58.6	113.5	113.7	127.6	129.0
21[g]	72.1	93.8	37.4	29.4	60.6	37.5	61.3	113.6	113.7	128.4	129.7
22	69.1	87.6	46.5	28.7	62.8[b]	38.0	62.4[b]	107.8	111.7	126.2	127.1
23	68.8	97.5	45.5	28.7	62.8[b]	38.0	63.7[b]	108.4	112.0	126.8	128.4[e]
24	70.2	86.3	43.3	28.8	64.2	35.1	58.5	110.9	112.0	126.4	126.8

[a] Solvent: [D_6]DMSO (**6a**), $CDCl_3$ (**8a**, **14**, **15**, **22**–**24**) or CD_3OD (**16**, **18**, **20**, **21**). Other signals: 9-, 10-OCH_3: two lines at δ = 55.7–57.7; C-9, -10: two lines at δ = 146.8–149.7; aromatic carbon lines: C-1′ (4-N-phenyl): δ = 150.0–150.0; C-1′ (4-phenyl): δ = 141.1 (**18**), 140.2 (**21**), 139.6 (**23**); C-1′ (benzoyl): δ = 129.5–130.5; C-2′, -6′ (4-N-phenyl): δ = 124.9 (**6a**), 122.5 (**8a**, **14**, **15**); C-2′, -6′ (4-phenyl + benzoyl): δ = 127.7–129.6; C-4′ (4-N-phenyl): δ = 122.3 (**6a**), 123.0 (**8a**), 122.8 (**14**, **15**); C-4′ (benzoyl): δ = 132.6–133.4; C=O: δ = 166.2–166.4. – [b,c] Alternative assignments may also be possible. – [d] Overlapped by the m of the solvent. – [e] Hidden by an aromatic carbon line. – [f] Two overlapping lines. – [g] Assignments confirmed by DEPT measurements.

Table 3. Physical and analytical data of the prepared compounds

Compound	Yield[a] %	M.p. [°C]	Solvent	Formula (M.W.)	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4a	94 (A)	158–160	ethyl acetate	$C_{21}H_{26}N_2O_4S$ (402.51)	62.66	6.51	6.95	62.28	6.92	6.81
4b	87 (A)	134–135	ethyl acetate	$C_{17}H_{26}N_2O_4S$ (354.46)	57.60	7.39	7.90	57.69	7.60	8.17
4c	86 (A)	157–158	ethyl acetate	$C_{21}H_{32}N_2O_4S$ (408.55)	61.73	7.89	6.85	61.46	8.11	6.70
5a	93 (A)	159–161	ethanol	$C_{23}H_{30}N_2O_4S$ (430.56)	64.16	7.02	6.50	64.43	7.24	6.54
5b	74 (A)	118–120	benzene	$C_{19}H_{30}N_2O_4S$ (382.52)	59.65	7.90	7.32	58.27	8.27	7.37
5c	77 (A)	148–150	benzene	$C_{23}H_{36}N_2O_4S$ (436.61)	63.27	8.31	6.41	63.78	8.52	6.46
6a	84 (B)	208–210	ethanol	$C_{21}H_{24}N_2O_4$ (368.43)	68.46	6.56	7.60	68.20	6.82	7.71
6b	69 (B)	110–112	ethanol	$C_{17}H_{24}N_2O_4$ (320.39)	67.73	7.55	8.75	67.53	7.90	8.42
6c	81 (B)	175–177	ethanol	$C_{21}H_{30}N_2O_4$ (374.48)	67.35	8.07	7.48	67.43	8.27	7.71
7a	75 (B)	202–203	ethanol	$C_{23}H_{28}N_2O_4$ (396.48)	69.67	7.11	7.06	69.41	7.31	7.04
7b	65 (B)	146–148	ethyl acetate	$C_{19}H_{28}N_2O_4$ (348.44)	65.49	8.09	8.03	65.80	8.25	8.44
7c	69 (B)	185–186	ethyl acetate	$C_{23}H_{34}N_2O_4$ (402.53)	68.62	8.51	6.95	68.54	8.71	6.90
8a	83 (C) 34 (D)	186–187	ethanol	$C_{21}H_{24}N_2O_3S$ (384.49)	65.60	6.29	7.28	65.82	6.29	7.35
8b	65 (C)	164–166	ethyl acetate	$C_{17}H_{24}N_2O_3S$ (336.45)	60.68	7.18	8.32	60.51	7.45	7.98
8c	83 (C)	156–158	ethyl acetate	$C_{21}H_{30}N_2O_3S$ (390.54)	64.58	7.74	7.17	64.40	7.68	7.07
9a	75 (C)	190–191	ethanol	$C_{23}H_{28}N_2O_3S$ (412.54)	66.96	6.84	6.79	67.20	7.14	6.42
9b	60 (C)	141–143	ethyl acetate	$C_{19}H_{28}N_2O_3S$ (364.50)	62.60	7.74	7.69	62.36	7.97	7.70
9c	77 (C)	207–209	ethanol	$C_{23}H_{24}N_2O_3S$ (418.59)	65.99	8.18	6.69	65.62	8.04	6.43
12	87 (A)	155–157	ethanol	$C_{28}H_{30}N_2O_5S$ (506.61)	66.38	5.96	5.52	66.50	6.10	5.60
13	69 (A)	169–173	ethanol	$C_{28}H_{30}N_2O_5S$ (506.61)	66.38	5.96	5.52	66.29	6.16	5.61
14	58 (C)	189–193	ethanol	$C_{28}H_{28}N_2O_4S$ (488.60)	68.83	5.77	5.73	68.81	5.83	5.79
15	61 (C) 69 (E)	154–158	ethanol	$C_{28}H_{28}N_2O_4S$ (488.60)	68.83	5.77	5.73	68.93	5.91	5.50
17	78 (F)	143–147	ethanol/ether	$C_{17}H_{25}NO_4$ (307.39)	66.42	8.19	4.55	66.15	8.46	4.68
18	75 (H)	169–171	b)	$C_{21}H_{25}NO_4$ (335.43)	70.96	7.08	3.94	71.19	7.23	4.12
19	70 (H)	95–97	b)	$C_{23}H_{29}NO_4$ (383.49)	72.03	7.62	3.65	71.82	7.58	3.54
20	82 (F)	125–127	acetone/ether	$C_{15}H_{21}NO_4$ (279.34)	64.50	7.58	5.01	64.82	7.29	5.16
21	9 (H)	151–154	ether	$C_{21}H_{25}NO_4$ (355.43)	70.96	7.08	3.94	70.84	7.20	3.99
22	64 (E)	142–143	ethanol	$C_{22}H_{25}NO_5$ (383.44)	68.91	6.57	3.65	69.07	6.88	3.73
23	76 (E) 61 (H)	118–121	ethyl acetate	$C_{28}H_{29}NO_5$ (459.54)	73.18	6.36	3.04	73.04	6.44	3.14
24	80 (F)	133–135	b)	$C_{22}H_{25}NO_5$ (383.44)	68.91	6.57	3.65	68.70	6.67	3.43

[a] Method of preparation in parentheses. – [b] Diisopropyl ether.

Experimental

The IR spectra of KBr pellets were measured with an Aspect 2000 computer-controlled Bruker IFS-113v FT spectrometer. – The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5-mm tubes at room temp. with a Bruker WM-250 or WP-80-SY FT spectrometer at 250.13 and 20.14 MHz, respectively, using the ^{2}H signal of the solvent as look and TMS as internal standard. The 2D-COSY and 2D-NOESY measurements were carried out using the standard software written for the Aspect 2000 computer of the spectrometer. – The isothiocyanates and aldehydes were commercial products. The amino alcohols **2** and **3** were prepared according to a literature method[11].

Thioureas **4a–c**, **5a–c**. – *Method A:* The dihydroxy compound **2** or **3** (10 mmol) was suspended in benzene (50 ml), the isothiocyanate (10 mmol) was added, and the mixture was heated at reflux for 1 h. After evaporation of the solvent, the desired compounds were obtained.

Isoureas **6a–c**, **7a–c**. – *Method B:* The thiocarboxamide derivative **4** or **5** (5 mmol) was stirred with methyl iodide (1.42 g, 10 mmol) in MeOH (15 ml) at room temp. for 3 h. After evaporation of the solvent, the oily residue was stirred for 3 h in MeOH (50 ml) containing KOH (6 g). The mixture was then evaporated, and water (20 ml) was added. The product was separated by extraction with chloroform (3 × 20 ml).

Isothioureas **8a–c**, **9a–c**. – *Method C:* Thiocarboxamide **4** or **5** (5 mmol) was heated at reflux for 30 min in ethanol (30 ml) containing 10% dry hydrogen chloride. After evaporation of the solvent, the residue was dissolved in water and neutralized with $NaHCO_3$. The thiazine **8a** was extracted with chloroform (3 × 20 ml).

Method D: Oxazinoisoquinoline **6a** (1.84 g, 5 mmol) was homogenized with P_2S_5 (5 g) and heated at 170°C for 3 h. The glass-like product was extracted with chloroform (3 × 20 ml). The combined extracts were dried and evaporated. The oily residue was purified on Al_2O_3 (50 g, activity II). Elution with 500 ml of petroleum ether/benzene (2:1) yielded 0.65 g (34%) of pure **8a**.

Attempted Ring Closure of Thioureas **12** *and* **13**: During the reaction of thiocarboxamide **12** or **13** (5 mmol) by method B, debenzoylation took place, and oxazinoisoquinoline **6a** was obtained in 42 and 49% yield, respectively.

Preparation of Benzoyloxy Derivative **15**. – *Method E:* Thiazine derivative **8a** (1.15 g, 3 mmol) was heated at reflux with benzoyl chloride (0.46 g, 3 mmol) in pyridine (20 ml) for 2 h. The mixture was then poured onto ice (100 g) and allowed to stand for ca. 12 h, yielding 1.01 g (69%) of crystalline **15**.

Alcohol **20**. – *Method F:* Amino alcohol **2** (1.34 g, 5 mmol) was heated at reflux with paraformaldehyde (0.20 g) in ethanol (25 ml). After evaporation of the mixture, the oily residue was triturated with ether, yielding 1.15 g (82%) of crystalline **20**.

Method G: Amino alcohol **2** (1.34 g, 5 mmol) was stirred with aqueous formaldehyde (10 ml, 37%) for 30 min. The reaction mixture was basified with aqueous NaOH (10 ml, 30%), and product **20** was extracted with ethyl acetate (3 × 25 ml), yielding 1.05 g (75%).

Alcohols **18**, **21**. – *Method H:* Amino alcohol **2** (1.35 g, 5 mmol) and benzaldehyde (0.53 g, 5 mmol) in ethanol (20 ml) were heated at reflux for 2 h. The solvent was evaporated, and the oily residue was triturated with ether, resulting in the crystalline 1,3-oxazine **18** (1.26 g, 75%), which was filtered off. On evaporation of the ethereal mother liquor, the C-1 epimer **21** (0.16 g, 9%) was obtained.

Table 4. Fractional coordinates of nonhydrogen atoms for **18** with e.s.d.'s in parentheses

Atom	x/a	y/b	z/c
O(3)	0.5446(1)	0.7207(1)	0.1875(1)
O(9)	0.8507(1)	0.2913(1)	0.5925(1)
O(10)	0.9273(1)	0.4653(1)	0.6315(1)
O(12)	0.9128(1)	0.6774(1)	0.2377(1)
N(5)	0.5247(1)	0.5706(1)	0.2695(1)
C(1)	0.7117(2)	0.6709(1)	0.3207(1)
C(2)	0.6377(2)	0.7540(1)	0.2680(1)
C(4)	0.4551(2)	0.6561(1)	0.2261(1)
C(6)	0.4378(2)	0.4952(1)	0.3004(1)
C(7)	0.5139(2)	0.4041(1)	0.3233(1)
C(7a)	0.6283(1)	0.4223(1)	0.4005(1)
C(8)	0.6877(2)	0.3455(1)	0.4570(1)
C(9)	0.7879(2)	0.3613(1)	0.5320(1)
C(10)	0.8314(1)	0.4557(1)	0.5521(1)
C(11)	0.7755(2)	0.5307(1)	0.4950(1)
C(11a)	0.6741(1)	0.5149(1)	0.4179(1)
C(11b)	0.613282)	0.6006(1)	0.3593(1)
C(12)	0.7993(2)	0.6228(1)	0.2490(1)
C(13)	0.3558(2)	0.6309(1)	0.1378(1)
C(14)	0.3939(2)	0.5929(2)	0.0474(1)
C(15)	0.3030(2)	0.5651(2)	-0.0311(2)
C(16)	0.1744(2)	0.5734(2)	-0.0204(2)
C(17)	0.1352(2)	0.6123(2)	0.0692(2)
C(18)	0.2260(2)	0.6408(2)	0.1474(2)
C(19)	0.8118(3)	0.1949(2)	0.5720(2)
C(20)	0.9569(2)	0.5602(2)	0.6661(2)

Attempted Ring Closure of **11** *with Benzaldehyde:* The *threo-O*-acyl derivative **11** (0.78 g, 2 mmol) was treated with benzaldehyde according to method H. After evaporation of the solvent, the oily residue was triturated with ether; the benzoate of amino alcohol **2** crystallized (0.18 g, 23%, mp 169–174°C). After evaporation of the ethereal solution during standing for several days, the oxazinoisoquinoline **18** crystallized (0.11 g, 16%).

X-ray Structure Determination of **18**[27]: $C_{21}H_{25}NO_4$; M_r = 355.44; monoclinic; a = 10.416(1), b = 13.888(1), c = 13.022(1) Å; β = 95.67(1)°, V = 1874.5(5) Å^{-3}; $D_{calcd.}$ = 1.259 g·cm^3; Z = 4; $F(000)$ = 760; space group $P2_1/n$; μ = 6.7 cm^{-1} for Cu-K_α radiation. Intensities of 3743 unique reflections were collected with an Enraf-Nonius CAD-4 diffractometer in the range 1.5° < Θ < 75.0° with an ω-2Θ scan using graphite-monochromated Cu-K_α radiation. Cell constants were determined by least-squares refinement of 25 reflections. Three standard reflections were monitored every hour and showed no significant decrease during the exposure. After data reduction, 3525 reflections with $I > 3.0\sigma(I)$ were taken as observed. The phase problems were solved by direct methods using the MULTAN 82 program[28]. In the course of the isotropic least-squares refinement of the positional parameters of nonhydrogen atoms, an empirical absorption correction was calculated with the DIFABS program[29]. The minimum and maximum corrections were 0.6999 and 1.3578, respectively. The fractional coordinates of hydrogen atoms bound to carbon atoms were generated from assumed geometries, while the OH group was located in a difference Fourier map. The hydrogen positions were only included with a mean isotropic temperature factor (fixed as the B_{eq} of the adjacent atom + 1 Å^2) in the structure factor calculation. Full matrix refinement; $\Sigma w(\Delta F)^2$ was minimized for 236 parameters. Final R = 0.057, R_w =

0.117, R_{tot} = 0.059, S = 9.27, $w = [\sigma^2(F_o) + 0.25\,(pF_o)^2]^{-1}$, where p = 0.01. The highest peak in the final difference Fourier map was 0.45 e·Å^{-3}. Scattering factors were taken from standard tables[30]. All calculations were performed with a PDP 11/34 minicomputer with the use of the SDP system by Enraf-Nonius with local modifications.

CAS Registry Numbers

2: 109001-70-9 / **3**: 124481-99-8 / **4a**: 124482-00-4 / **4b**: 124482-01-5 / **4c**: 124482-02-6 / **5a**: 124482-03-7 / **5b**: 124482-04-8 / **5c**: 124482-05-9 / **6a**: 124482-16-2 / **6b**: 124482-17-3 / **6c**: 124482-18-4 / **7a**: 124482-19-5 / **7b**: 124482-20-8 / **7c**: 124482-21-9 / **8a**: 124482-22-0 / **8b**: 124482-23-1 / **8c**: 124482-24-2 / **9a**: 124482-25-3 / **9b**: 124482-26-4 / **9c**: 124482-27-5 / **10**: 113583-45-2 / **11**: 113583-46-3 / **12**: 124482-06-0 / **13**: 124482-07-1 / **14**: 124482-08-2 / **15**: 124482-09-3 / **16**: 124482-10-6 / **17**: 124482-11-7 / **18**: 124579-45-9 / **19**: 124579-46-0 / **20**: 124482-12-8 / **21**: 124579-47-1 / **22**: 124482-13-9 / **23**: 124482-14-0 / **24**: 124482-15-1 / PhCHO: 100-52-7 / PhNCS: 103-72-0 / EtNCS: 542-85-8 / cyclohexyl isothiocyanate: 112-82-3

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[282/89]